MILITARY PSYCHOLOGY, *10*(3), 173–193

# Modafinil During 64 Hr of Sleep Deprivation: Dose-Related Effects on Fatigue, Alertness, and Cognitive Performance

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Modafinil is a relatively new synthetic psychostimulant that has been shown to promote vigilance and arousal with apparently few physiological side effects. Accordingly, modafinil may provide a safe and effective alternative to the more

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DCIEM No. 96-P-45

102-00733/



commonly used amphetaminic class of stimulants, for example, in clinical settings to treat sleep disorders (e.g., idiopathic hypersomnia and narcolepsy) and sustained military operations to promote vigilance during periods of prolonged sleep deprivation. In this article, we investigate the relative effects of three doses of modafinil on fatigue and cognitive performance in a double-blind, placebo-controlled, 64-hr sleep-deprivation study. We observe a dose-related ordering on subjective measures of fatigue, motivation, subjective performance, and alertness following 4 min with eyes closed and on objective measures of serial reaction time, complex mental addition, and short-term memory. Specifically, 300 mg of modafinil in a 24-hr period (100 mg every 8 hr) was found to maintain cognitive performance at or near baseline levels throughout the sleep-deprivation period, 150 mg of modafinil in a 24-hr period (50 mg every 8 hr) provided some maintenance of performance, and 50 mg of modafinil in a 24-hr period (16.7 mg every 8 hr) was not substantively different from placebo. In addition, subjective reports made by the participants during weekly debriefings revealed no evidence of intolerance at any drug dose. Accordingly, these findings permit a specification of the minimum dose of modafinil required for the safe and effective amelioration of cognitive performance decrements induced by a period of prolonged sleep deprivation.

Modafinil (diphenylmethyl-sulfinyl-2 acetamide) is a relatively new synthetic stimulant that has become the focus of intensive research in recent years. Developed in France by Laboratiore L. Lafon, modafinil has attracted a burgeoning interest based primarily on a growing body of evidence that suggests that the compound promotes vigilance and arousal without toxicity, tolerance, dependency, or significant sleep disturbances (Laboratiore L. Lafon, 1994). Accordingly, modafinil may provide a safe and effective alternative to the traditionally used amphetaminic class of compounds, which are known to be associated with various physiological and behavioral side effects (e.g., cardiovascular effects, tolerance, addiction, and disturbed sleep; see Angrist, Corwin, Bartlik, & Cooper, 1987; Hart & Wallace, 1975; Hartmann & Cravens, 1976; Newhouse et al., 1989, Newhouse et al., 1992; Penetar et al., 1991; Warot, Corruble, Payan, Weil, & Fuech, 1993).

Although the specific mode of action for modafinil is not fully understood to date (see Mignot, Nishino, Guilleminault, & Dement, 1994), the consensus of numerous researchers is that the arousal-inducing effect derives from the stimulation of central alpha 1 adrenergic receptors (for a review, see Buguet, Montmayeur, Pigeau, & Naitoh, 1995; Lagarde & Batejat, 1995). Accordingly, several studies have now shown that modafinil's behavioral (Buguet et al., 1995; Pigeau et al., 1995; Saletu et al., 1989), subjective (Baranski & Pigeau, 1997; Warot et al., 1993), and pharmacological (e.g., De Séréville, Bore, Rambert, & Duteil, 1994; Duteil, Rambert, Pessonnier, Gombert, & Assous, 1979; Duteil et al., 1990; Hermant, Rambert, & Duteil, 1991; Lagarde, 1990; Lin et al., 1992; Rambert, Pessonnier, & Duteil, 1990; Shelton, Nishino, Vaught, Dement, & Mignot, 1995; Simon, Panissaud, & Costentin, 1994) properties are clearly distinct from that of amphetamine.

Despite the current lack of a substantiated theory of modafinil's underlying mechanism, the relatively benign pharmacological effects of the drug, coupled with its vigilance-promoting properties, have recently stimulated two distinct avenues of research involving human participants. First, modafinil has been shown to provide successful, long-term treatment of clinical sleep disorders such as idiopathic hypersomnia and narcolepsy (e.g., Bastuji & Jouvet, 1988; Billiard et al., 1994; Boivin, Montplaisir, Petit, Lambert, & Lubin, 1993; Laffont, Mayer, & Minz, 1994). Second, the utility of modafinil is currently being investigated in the context of sustained military operations (see Lagarde & Batejat, 1995; Lyons & French, 1991) as a potential countermeasure to the effects of extensive sleep deprivation on human cognitive performance (for reviews of various portions of the sleep-deprivation and performance literature, see Angus, Pigeau, & Heslegrave, 1992; Babkoff, Caspy, Mikulincer, & Sing, 1991; Dinges & Kribbs, 1991; Hockey, 1986; Krueger, 1989, 1991). In fact, modafinil was used by French military forces personnel during Operation Desert Storm (Lagarde, Louisy, & Matton, 1991).

To date, results bearing on the effectiveness of modafinil on cognitive performance during sleep deprivation have been encouraging. Bensimon et al. (1991) compared a single dose of modafinil (200 mg) to a placebo in 12 adults during a single night of sleep deprivation. Participants received the drug at 2200 and were tested 6 and 18 hr later (at 0400 and 1600) on a series of cognitive and psychomotor tasks. The results showed a beneficial effect of modafinil on reaction time and short-term memory at 6-hr postdose; at 18-hr postdose, the effects were not different from the placebo.

Lagarde and Batejat (1995) tested 8 adults in a comparison of the placebo and modafinil (600 mg over a 24-hr period, divided into 3 daily doses of 200 mg) in a 60-hr sleep-deprivation study. Doses were administered at 2200, 0600, and 1400. Three, 1-hr psychological performance testing sessions occurred daily at (approximately) 0900, 1700, and 0300. The results showed clear performance decrements induced by sleep deprivation in the placebo condition. However, participants in the modafinil condition were able to maintain their performance at baseline levels until the 44th hr of sleep deprivation.

Most recently, Pigeau et al. (1995) compared the effectiveness of modafinil (300 mg; $n = 14$) with that of d-amphetamine (20 mg; $n = 13$) and placebo ($n = 13$) in a 64-hr sleep-deprivation study requiring continuous cognitive work. Drugs were administered three times during the sleep-deprivation period: (a) at 2330 of the 1st night of sleep deprivation to determine if the stimulants could maintain performance through the anticipated "first-night dip," which is common in experiments requiring continuous cognitive work; (b) at 0530 of the 3rd day of sleep deprivation to determine the recuperative effects of the stimulants; and (c) at 1730 of the 3rd day of sleep deprivation to investigate the effects of the stimulants on recovery sleep and sleep physiology (see Buguet et al., 1995). Briefly, the results showed that (a) the cognitive maintenance and recuperative effects of modafinil paralleled closely

with that of d-amphetamine but with significantly fewer reported physical side effects (Pigeau et al., 1995); and (b) modafinil, unlike d-amphetamine, did not have an antagonistic effect on recovery sleep (Buguet et al., 1995).

## THIS STUDY

Modafinil can effectively ameliorate cognitive performance deficits due to sleep deprivation. However, in each of those studies, the single-dose administrations were between two and three times higher than those currently being employed in the treatment of clinical hypersomnia and narcolepsy (e.g., Laffont et al., 1994). Indeed, in clinical populations, low single-dose administrations of modafinil (e.g., 100 mg) have yielded no reports of intolerance to date, even following long-term treatment (3–8 years). On the other hand, at relatively high doses (600–800 mg/day), modafinil has shown a dose-dependent effect on blood pressure, anxiety, and insomnia (Laboratiore L. Lafon, 1994). In addition, a single dose of 200 mg has been shown to affect thermoregulation during cold exposure (Bourdon, Jacobs, Bateman, & Vallerand, 1994), and a single-dose of 300 mg has been shown to antagonize supine pulse rate (Warot et al., 1993), frequency of urination (Pigeau et al., 1995), incidence of headache (Warot et al., 1993), efficiency of communicated speech (Bard, Sotillo, Anderson, Thompson, & Taylor, 1996), and subjective estimates of cognitive capability (Baranski & Pigeau, 1997). Accordingly, if modafinil is to be considered for use in sustained military contexts, then it is important to determine the minimum dose that can ensure safe, operational effectiveness.

This study reports the results of a double-blind, placebo-controlled manipulation of three relatively low doses of modafinil on subjective fatigue, alertness, and cognitive performance during 64 hr of sleep deprivation. To gauge the relative efficacy of the three doses, we employed a preventive paradigm (see Babkoff & Krueger, 1992) in which modafinil or the placebo was administered at 8-hr intervals throughout the sleep-deprivation period. For logistical reasons (e.g., periodic medical examinations such as blood, urine, and thermoregulatory tests and electrocardiogram analyses), we could not employ a continuous cognitive work paradigm (e.g., Pigeau et al., 1995). However, the cognitive work–rest ratio schedule employed in this study was considerably higher than those employed in related studies (e.g., Bensimon et al., 1991; Lagarde & Batejat, 1995).

## METHOD

### Participants

Six members of a French Army artillery unit participated for four 1-week testing sessions in return for Fr 6,000. All participants were men between 20 and 24 years

old, were prescreened by a physician, and were classified as fit to participate if they met the following criteria: (a) were healthy; (b) were medication free for at least 3 weeks prior to the experiment; (c) had normal or corrected-to-normal vision; and (d) had no allergies or hematological, cardiovascular, neurological, psychiatric, or sleep-related disorders. All participants were fully informed about the purposes of the study and the procedures to be employed, signed informed consent forms for participation, and were given a full debriefing and a medical examination on completion of the study. The experiment was approved by the Centre de Recherches du Service de Santé des Armées (CRSSA) ethics committee for research involving human participants.

## Materials

Psychological testing was carried out in the Department of Psychology at CRSSA. Six testing stations were used to investigate preattentional and attentional vision, mental rotation, mental imagery, spatial orientation, visual guidance, and fundamental cognitive processes. Only results for the latter cognitive test battery are reported in this article; results for the remaining psychological tests will be reported in future reports. For the cognitive testing sessions, participants worked independently in a 4 m × 5 m office that was prepared for experimentation. All tasks and questionnaires were performed on a 90 MHz Pentium computer and were displayed on a Phillips 17-in. color monitor. The computer mouse was used as an input device.

## Procedure

The study employed a double-blind, fully within-subject manipulation of three doses of modafinil and the placebo. Participants participated under the influence of a different drug dose in each of the 4 weeks of testing: 300 mg within a 24-hr period (100 mg/8 hr), 150 mg within a 24-hr period (50 mg/8 hr), 50 mg within a 24-hr period (16.7 mg/8 hr), and the placebo, respectively. Each week of testing was separated by a 2-week drug "wash-out" period. Drug doses were counterbalanced over participants and weeks according to a Latin-square design. Daily doses were delivered at 8-hr intervals during the sleep-deprivation period (i.e., at 2000, 0400, and 1200), beginning on the 1st night of sleep deprivation and continuing through to the 3rd day of sleep deprivation (see Figure 1).

Psychological testing sessions comprised 24 hr of the 64 hr sleep-deprivation period (i.e., six sessions of 4 hr duration). During periods of inactivity, participants read, watched television and movies, and participated in a variety of nonphysically demanding games (e.g., video games, cards, etc.). Participants were permitted to leave the facility to take walks while under the supervision of an experimenter. Numerous physiological measures were recorded throughout the study (e.g.,

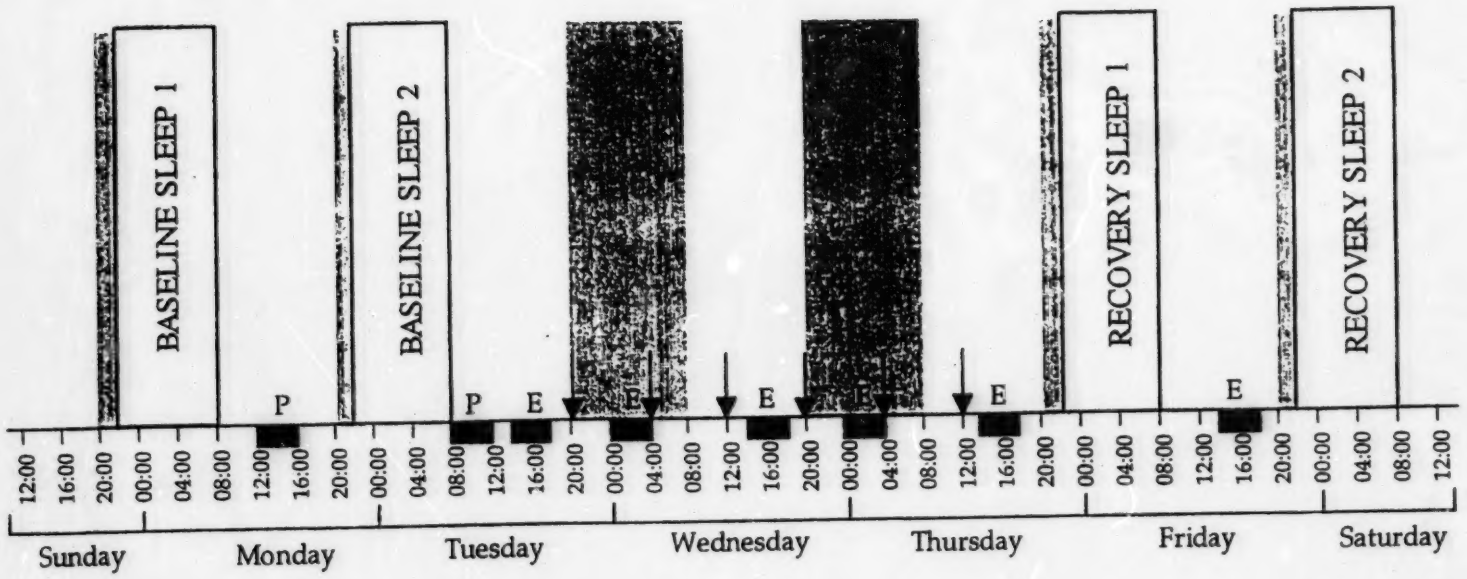



FIGURE 1 Graphical description of the experimental time line. Large shaded bars denote evening periods (2000–0800), and large open bars denote time spent asleep. Arrows indicate times at which the drug was administered. Small filled boxes represent 4-hr sessions of psychological testing. The letter *P* denotes practice sessions, and the letter *E* denotes experimental testing sessions.

electroencephalogram, heart rate, blood pressure, blood and urine samples, and core body temperature); these data will be reported elsewhere by the CRSSA Thermophysiology and Vigilance Physiology groups (e.g., Buguet, Fidier, Roux, & Montmayeur, 1996).

There were eight psychological testing sessions each week; the first two sessions (Monday afternoon and Tuesday morning) were considered practice and were not analyzed. Each session lasted approximately 4 hr (see Figure 1) and involved 40 min of testing at each of the six stations previously discussed. The order of the testing stations was counterbalanced over participants, sessions, and weeks according to a Latin-square design.

## Cognitive Test Battery

The cognitive test battery included a subset of tasks that have been used extensively in previous sleep loss and performance studies conducted at the Defence and Civil Institute of Environmental Medicine (e.g., Angus & Heslegrave, 1985; Baranski, Pigeau, & Angus, 1994; Heslegrave & Angus, 1985; Pigeau et al., 1995). The tasks selected for study were chosen so as to permit the investigation of a diverse range of fundamental cognitive processes under the 40-min time constraint permitted by the design. The test battery included:

- *Four-Choice Serial Reaction Time (3 min):* On each trial, four response buttons (*P, G, L,* and *S*) were presented on the computer monitor in a square configuration (i.e., two above and two below). Directly above the displayed letters, a probe letter (*P, G, L,* or *S*) was presented. The participants' task was to move a visual pointer with the mouse over the corresponding probe letter and to depress the mouse button as quickly and as accurately as possible. The probe letter varied on each trial and was randomly generated by the program. Response times were recorded from the appearance of the probe letter to the depression of the response button on the mouse.
- *(Visual) Perceptual Comparison (5 min):* The comparison task required the relative judgment of line length. Each trial began with the presentation of an instruction ("LONGER" or "SHORTER"), which was displayed near the top of the computer monitor. One second later, the visual display appeared, which consisted of two horizontal lines, divided by one short vertical line. The display remained on the screen for the participant until he responded. The participant's task was to determine which of the two lines was longer or shorter, depending on the instruction. Participants responded by depressing either the left or the right button on the mouse to indicate that the left or right line was the longest or the shortest. Four levels of judgment difficulty were randomly presented to the participants; we defined the difficulty a priori on the basis of the ratio of the longest to the shortest

line (1.03, 1.05, 1.07, and 1.09). All lines appeared black on a white background. Participants were encouraged to respond as quickly and as accurately as possible. Feedback on the accuracy of the judgments was not provided.

• *Mental Addition (9 min):* The addition task required participants to add a random sequence of eight numbers (1–16) that were presented on the computer monitor at a rate of one number every 1.25 sec. The sequence was terminated by the presentation of a visual prompt (⇒) at which time participants typed in their response using the mouse and a visual keypad presented on the monitor. As with the comparison task, feedback on the accuracy of the judgments was not provided at any point during the study.

• *Short-Term Memory (Digit Span; 5 min):* Participants were presented with strings of numerical digits to memorize. Each digit was presented for 1 sec; then, 0.5 sec later, the next digit was presented. The participant's task was to memorize the complete string of digits and to recall the string immediately after the last digit was presented. Participants recalled the digits by clicking the appropriate numbers with the mouse on a visual keypad presented on the monitor. Recall was required either in the same or the opposite order to the presentation. If the participants answered correctly, then the digit string was increased by 1 digit; if the string was recalled incorrectly, then the subsequent string was decreased by 1 digit.

• *Subjective Questionnaire (≈1 min):* The questionnaire included four items that probed the participant's current level of fatigue, motivation, mood, and performance. Each question involved an 11-point visual analogue scale, which was anchored at both ends by a short verbal description, from 0 (*not at all tired*) to 10 (*very tired*). The participant "hooked" a visual pointer on a sliding scale with the mouse and dragged the pointer to the appropriate location on the scale.

• *Alertness Following 4 Min With Eyes Closed (4 min):* The final task required the participant to sit erect in a comfortable position for 4 min with his eyes closed while attempting not to sleep (Pigeau, Heslegrave, & Angus, 1987). On completion of the 4-min period, participants responded to a single question that required them to estimate their subjective level of alertness during the period. The scale consisted of a 7-point Stanford Sleepiness scale (which was adapted for this task), where 1 was *I was alert and wide awake,* 2 was *I was alert, somewhat relaxed but not at my peak,* 3 was *I was very relaxed and even a bit drowsy,* 4 was *I was very drowsy and almost fell asleep,* 5 was *I was extremely drowsy and may have fallen asleep briefly,* 6 was *I fell asleep a number of times and it was difficult to stay awake even for short periods,* and 7 was *I fell asleep and stayed asleep until the task was over and I had to be awakened by the experimenter.* One objective of the 4-min eyes-closed task is to obtain more sensitive momentary subjective estimates of fatigue and sleepiness by counteracting the potentially arousal-inducing effects of the preceding cognitive tasks. Indeed, Pigeau et al. (1987) showed that subjective reports in this task are highly correlated with electrophysiological measures of drowsiness during the 4-min period.

## RESULTS

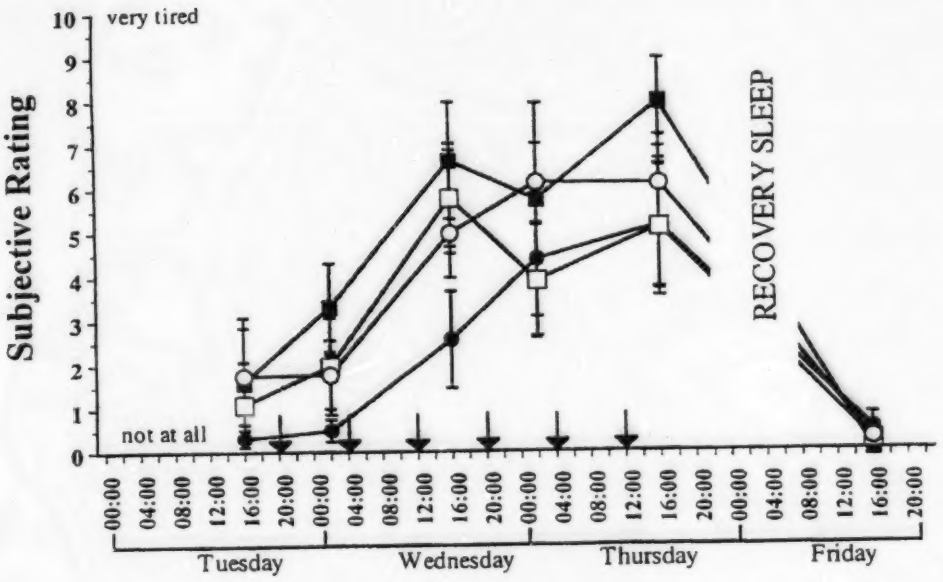
The results are reported in two sections. The first section reports the effects of the drug manipulation on subjective mood, fatigue, performance, motivation, and alertness following 4 min with eyes closed. The second section provides a view of the effects of the drug manipulation on performance in the cognitive test battery. All results were analyzed by repeated measures analysis of variance (ANOVA), with drug condition (four levels) and session (six levels) as within-subject factors. Unfortunately, 1 participant had to be excused from his 2nd week of testing (50 mg of modafinil within a 24-hr period) because of illness. Throughout, each ANOVA involved replacing his missing data by cell means for that condition. All ANOVAs were also conducted with that participant's entire data set excluded, and the interpretation of the results was the same in each case. Finally, all ANOVAs include an adjustment (i.e., reduction) to the degrees of freedom for the interaction term in order to reflect the fact that cell means were used (e.g., Winer, 1971).

### Subjective Measures

*Fatigue.* Panel A of Figure 2 provides the data for subjective estimates of fatigue. All conditions display an increase in fatigue during the sleep-deprivation period, with generally higher levels for the placebo and the 50 mg of modafinil within a 24-hr period than for the higher doses of modafinil. The ANOVA revealed a main effect of sessions, $F(5, 25) = 26.68$, $p < .0001$, confirming that fatigue increased during the sleep-deprivation period. The main effect of the drug condition was also significant, $F(3, 15) = 3.63$, $p < .05$, and planned comparisons revealed that the 300 mg of modafinil within a 24-hr period differed from the placebo, $F(1, 5) = 17.91$, $p < .01$, with this difference being most clearly evident the 1st night, $F(1, 5) = 7.64$, $p < .05$, and the 2nd day, $F(1, 5) = 7.19$, $p < .05$. The difference between the 300 mg of modafinil within a 24-hr period and the other modafinil doses was marginally significant during the 1st night and the 2nd day ($.05 < p < .10$).

*Motivation.* Panel B of Figure 2 provides a view of subjective estimates of motivation. Overall, motivation was quite high, with the placebo and 50 mg of modafinil within a 24-hr period showing some loss during the 2nd night and the 3rd day. The effect of sessions was significant, $F(5, 25) = 3.26$, $p < .025$. The effect of drug condition was marginally significant, $F(3, 15) = 2.87$, $p = .071$, and planned comparisons revealed that 300 mg of modafinil within a 24-hr period differed from the placebo, $F(1, 5) = 8.12$, $p < .05$, and was marginally different from 50 mg of modafinil within a 24-hr period ($p = .088$).

## A - Fatigue




## C - Mood

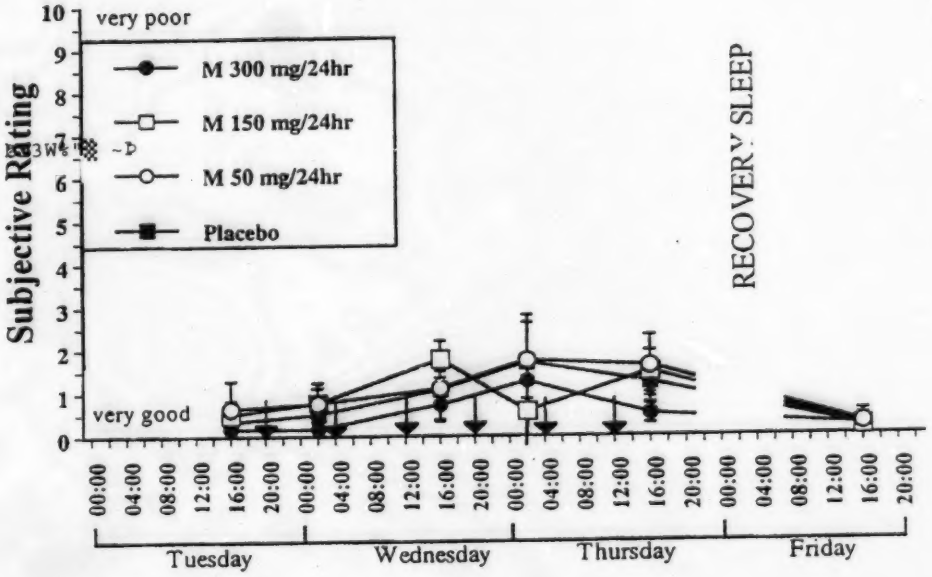



FIGURE 2 (Continued)

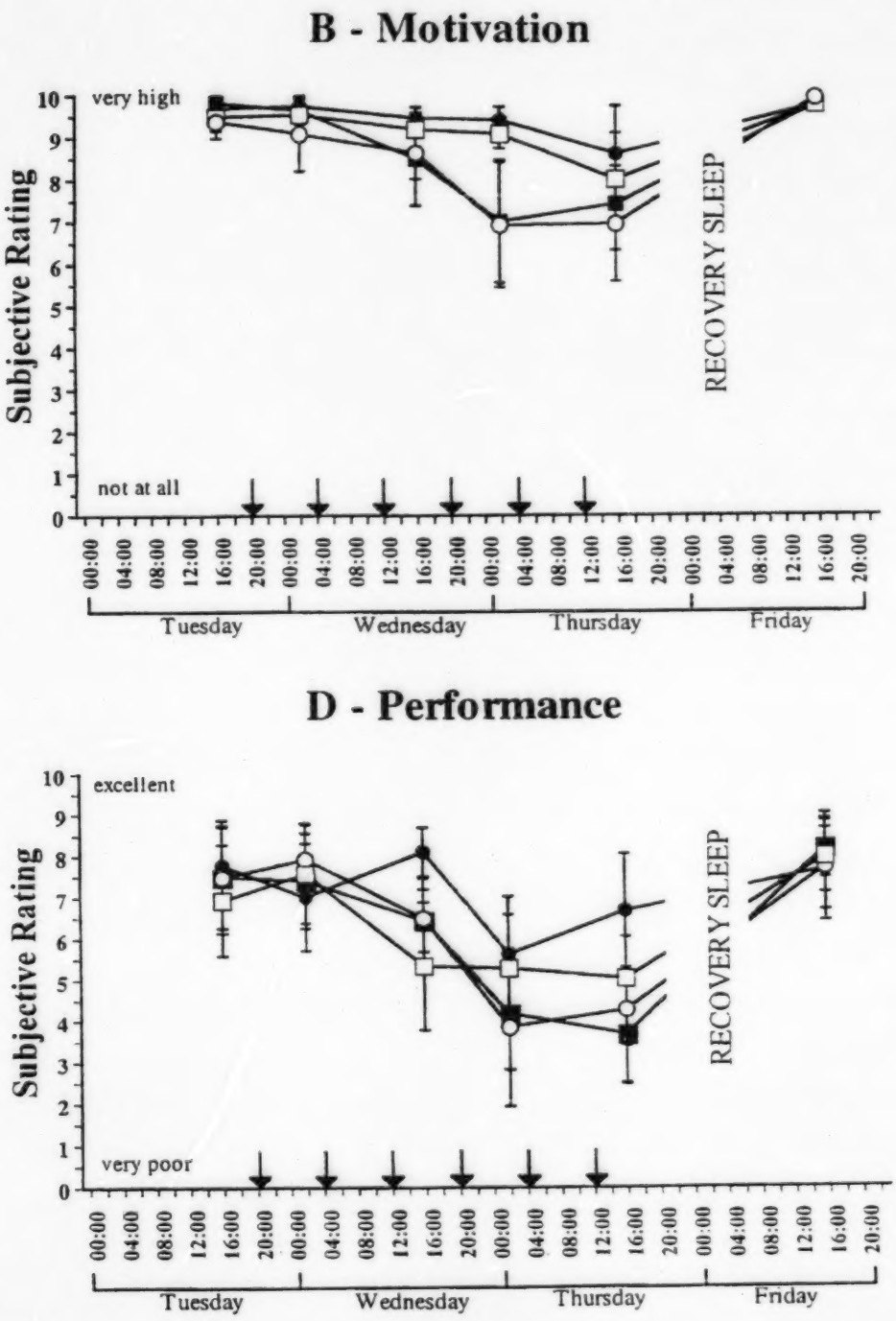



FIGURE 2 Subjective estimates of fatigue (Panel A), motivation (Panel B), mood (Panel C), and performance (Panel D) for the four drug conditions during the sleep-deprivation period. Large shaded bars denote evening periods (2000–0800). The arrows on the *x* axis denote the times at which drugs were administered. Error bars denote the standard error of measurement over participants.

*Mood.* Panel C of Figure 2 shows the data for subjective estimates of mood. Overall, these participants were quite amicable, although there was a slight deterioration in mood following the 2nd day of sleep deprivation. This result was substantiated by an effect of sessions, $F(5, 25) = 3.77$, $p < .01$. No main effects or interactions involving the drug condition were evident.

*Performance.* Panel D of Figure 2 provides a view of subjective estimates of performance during the week. Overall, the 300 mg of modafinil within a 24-hr period shows some advantage throughout the sleep-deprivation period, whereas the placebo and the 50 mg of modafinil within a 24-hr period show the largest decrement. ANOVA revealed an effect of sessions, $F(5, 25) = 8.16$, $p < .0001$. Although no effects involving drug dose were significant, an a priori comparison revealed a significant difference between the placebo and 300 mg of modafinil within a 24-hr period, $F(1, 5) = 6.84$, $p < .05$.

*Alertness following 4-min eyes closed.* Figure 3 provides a plot of subjective estimates of alertness following 4 min with eyes closed. The data display a clear dose-related ordering, particularly during the last three sessions of the sleep-deprivation period. The main effect of sessions was significant, $F(5, 25) = 17.40$, $p < .0001$, as was the effect of the drug condition, $F(3, 15) = 3.75$, $p < .034$. Planned contrasts revealed that the placebo differed from the 300 mg of modafinil within a 24-hr period during the 2nd night, $F(1, 5) = 12.27$, $p < .025$, and the 3rd day, $F(1, 5) = 11.36$, $p < .025$.

## Cognitive Performance Measures

*Serial reaction time.* A preliminary analysis revealed no evidence of a speed–accuracy tradeoff effect during the sleep-deprivation period. Accordingly, Panel A of Figure 4 reports the number of correct responses per minute, which provides a composite measure of response speed and accuracy. Overall, the 300 mg of modafinil within a 24-hr period effectively maintained performance throughout the sleep-deprivation period, whereas the other conditions display a deterioration during the 2nd night; on the 3rd day, only the placebo condition shows continued impairment. The main effect of sessions was significant, $F(5, 25) = 16.46$, $p < .0001$. The main effect of the drug condition was not significant, but the Drug × Session interaction was significant, $F(15, 69) = 2.73$, $p < .01$. Planned contrasts revealed a difference between 300 mg of modafinil within a 24-hr period and 50 mg of modafinil within a 24-hr period during the 2nd night, $F(1, 5) = 11.63$, $p < .025$. On the 3rd day, the placebo differed from 300 mg of modafinil within a 24-hr period, $F(1, 5) = 9.59$, $p < .025$, and differed marginally from 150 mg of modafinil within a 24-hr period ($p = .087$).

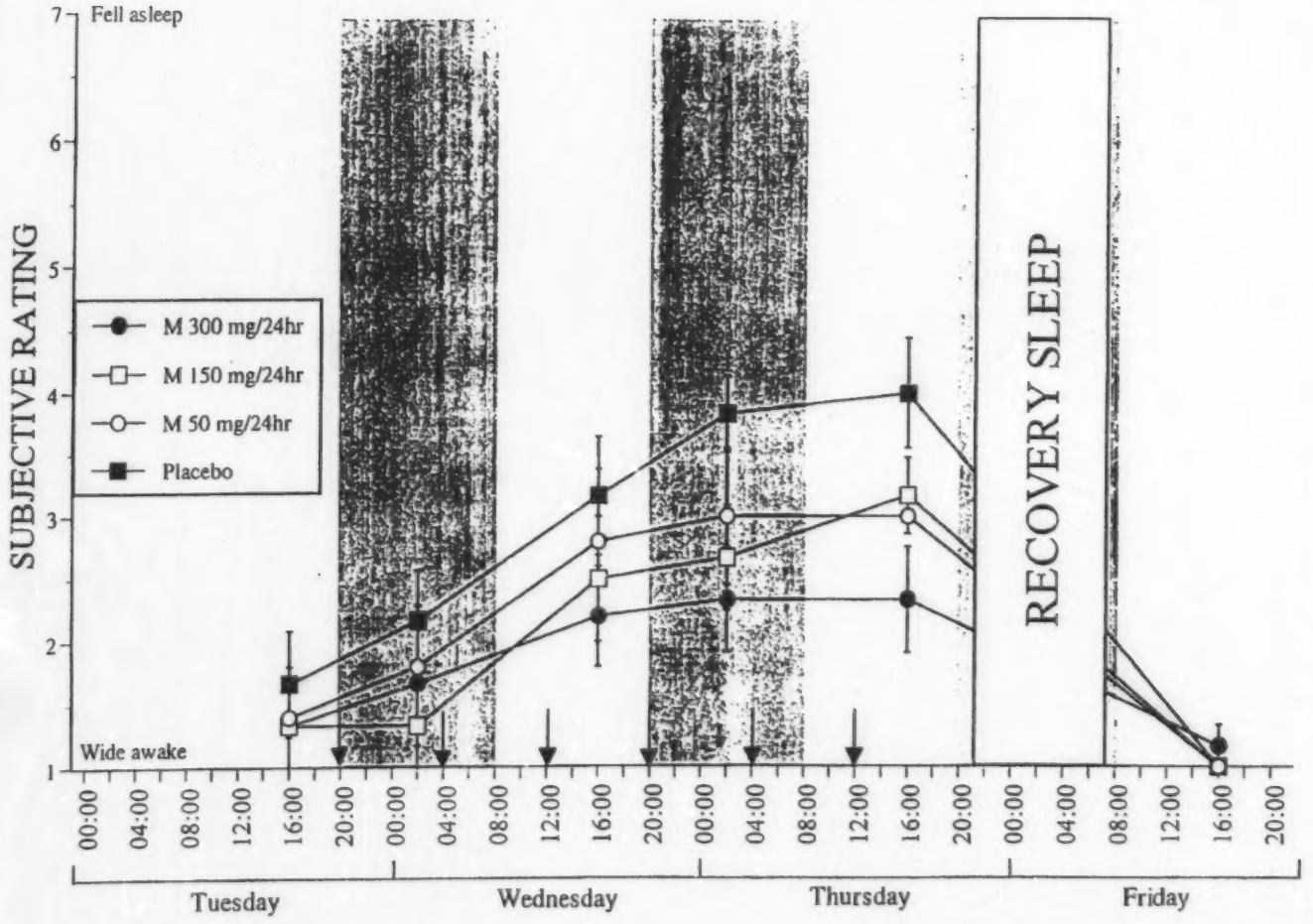
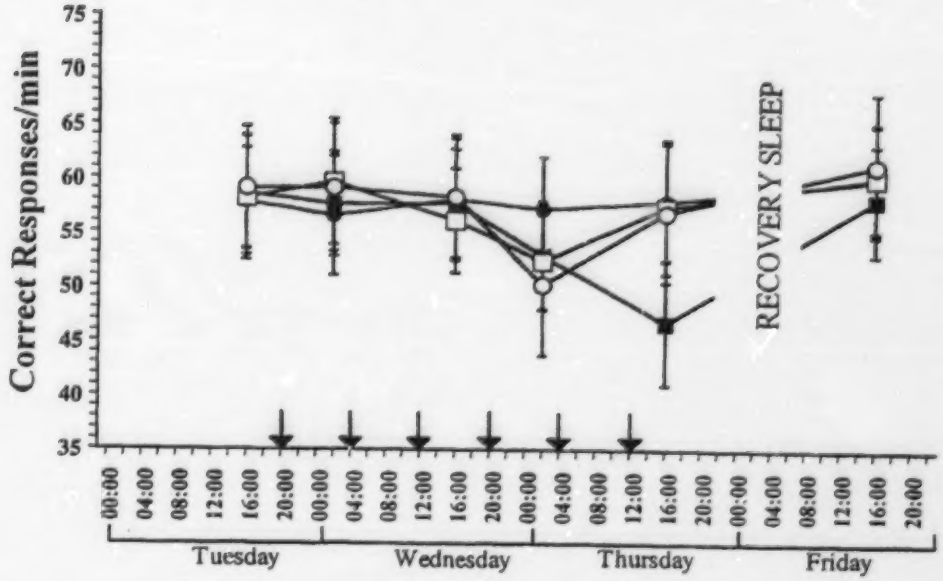



FIGURE 3 Level of alertness following 4 min with eyes closed for the four drug conditions during the sleep-deprivation period. Large shaded bars denote evening periods (2000–0800). The arrows on the *x* axis denote the times at which drugs were administered. Error bars denote the standard error of measurement over participants.

## A - Serial Reaction Time




## C- Short-Term Memory

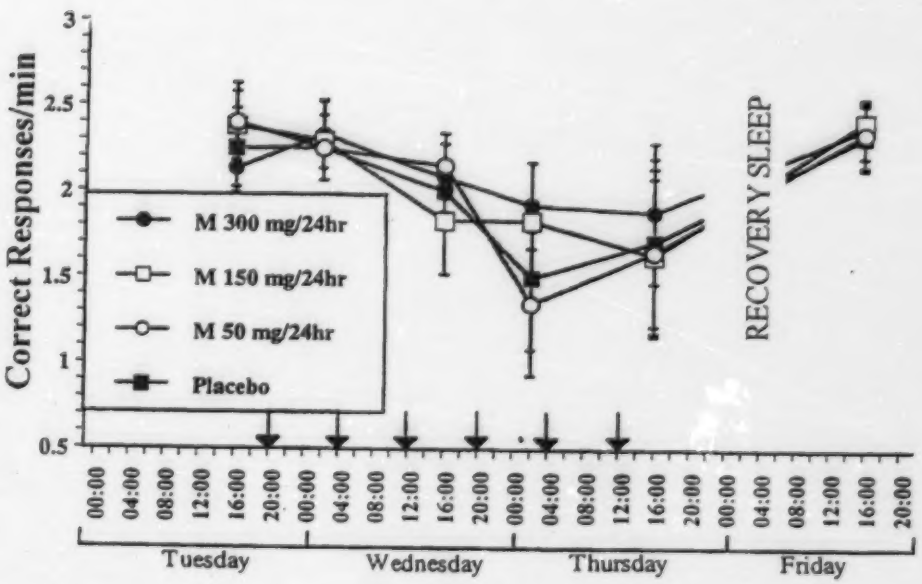



FIGURE 4 (Continued)

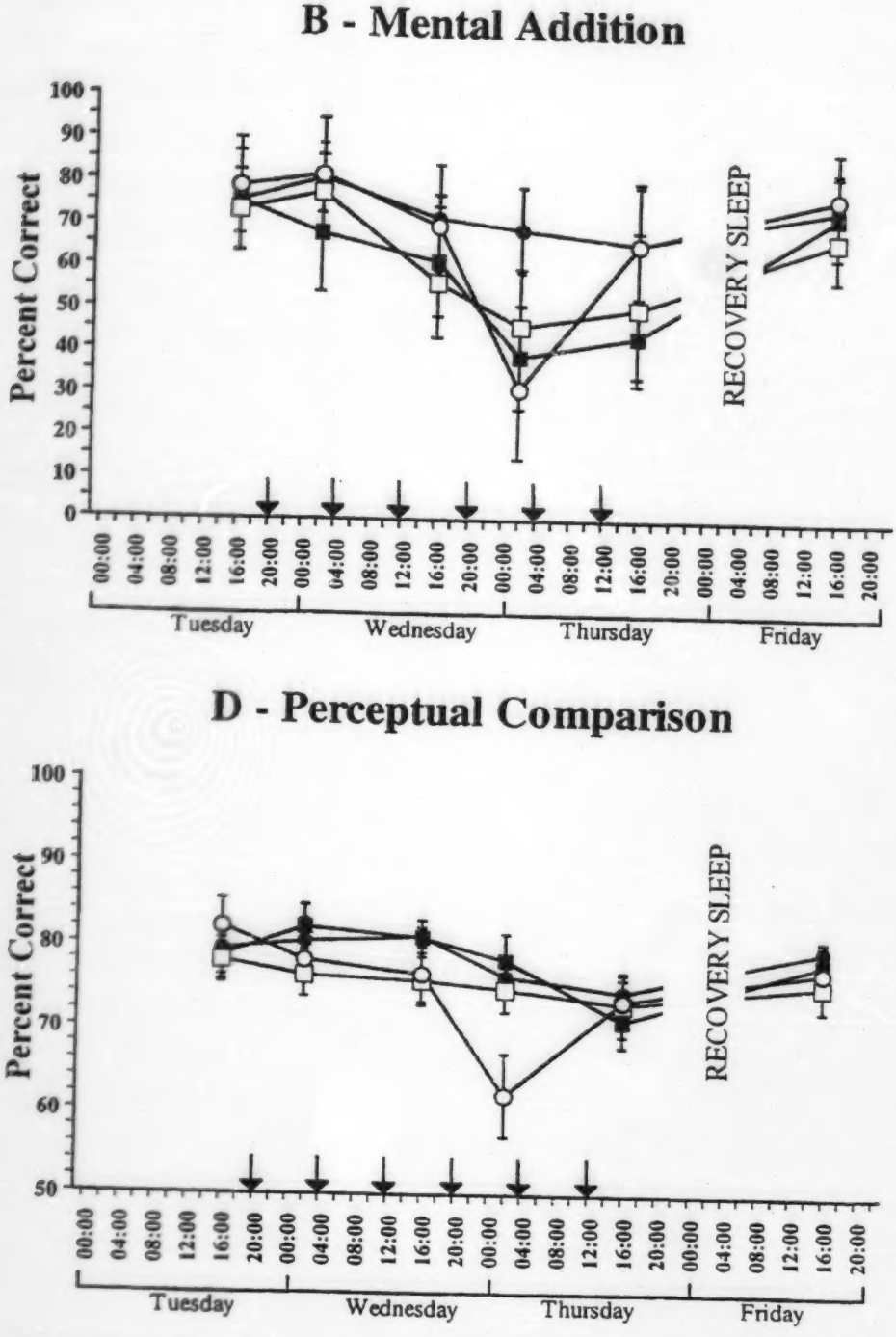



FIGURE 4 Performance on the serial reaction time task (Panel A), mental addition task (Panel B), short-term memory task (Panel C), and perceptual comparison task (Panel D) for the four drug conditions during the sleep-deprivation period. Large shaded bars denote evening periods (2000–0800). The arrows on the *x* axis denote the times at which drugs were administered. Error bars denote the standard error of measurement over participants.

*Mental addition.* Panel B of Figure 4 provides the data for the mental addition task. Once again, 300 mg of modafinil within a 24-hr period effectively maintains performance throughout the sleep-deprivation period. In contrast, the other conditions show a deterioration during the 2nd night with a small circadian recovery on the 3rd day. Both main effects were significant—for sessions, $F(5, 25) = 9.25$, $p < .0001$, and for drug, $F(3, 15) = 3.39$, $p < .05$—as was the Drug × Session interaction, $F(15, 69) = 1.86$, $p < .05$. Planned contrasts revealed a difference between the placebo and 300 mg of modafinil within a 24-hr period, $F(1, 5) = 39.04$, $p < .005$; this difference was marginally evident the 1st night ($p = .081$) but was clearly evident the 2nd day, $F(1, 5) = 14.11$, $p < .025$; the 2nd night, $F(1, 5) = 28.64$, $p < .005$; and the 3rd day, $F(1, 5) = 11.22$, $p < .025$. There was also a marginal difference between 300 mg of modafinil within a 24-hr period and 50 mg of modafinil within a 24-hr period the 2nd night, $F(1, 5) = 6.08$, $p = .057$, and a significant difference between the placebo and 50 mg of modafinil within a 24-hr period on the 3rd day, $F(1, 5) = 20.85$, $p < .005$.

*Short-term memory.* Panel C of Figure 4 provides the data for the short-term memory task. A number of dependent measures were investigated (e.g., correct responses, response time, and maximum string length attained), with none emerging more highly sensitive to performance changes in this task. Hence, Panel C presents data on the number of correct responses per minute, which provides a composite measure of response speed and accuracy. The data show trends that closely parallel those of the mental addition task: Performance in the 300 mg of modafinil within a 24-hr period is superior, and the placebo and low-dose modafinil condition show an impairment the 2nd night and the 3rd day. However, higher between-subject variability obviated the statistical detection of these effects. Thus, the only significant effect emerging from the analysis was the main effect of sessions, $F(5, 25) = 5.47$, $p < .005$.

*Perceptual comparison.* Panel D of Figure 4 provides a plot of the percentage of correct responses in the perceptual comparison task. A preliminary analysis showed that each level of judgment difficulty displayed similar trends across sessions; thus, the results are averaged over the four levels of judgment difficulty. Overall, the data show a small but general decline in performance for all conditions. In addition, the drug manipulation was unremarkable, except for the clear decrement in the 50 mg of modafinil within a 24-hr period during the 2nd night. The main effect of sessions was significant, $F(5, 25) = 7.27$, $p < .0005$. The main effect of the drug condition was not significant, but the Drug × Sessions interaction was significant, $F(15, 69) = 1.91$, $p < .05$. Planned comparisons revealed that, on the 2nd night, the 50 mg of modafinil within a 24-hr period differed from the placebo

condition, $F(1, 5) = 12.22$, $p < .025$, and the 300 mg of modafinil within a 24-hr period, $F(1, 5) = 9.60$, $p < .025$, and was marginally different from the 150 mg of modafinil within a 24-hr period, $F(1, 5) = 6.46$, $p = .052$.

The substantial decline in the 50 mg of modafinil condition on the 2nd night is anomalous, except for two further consistencies in the data. First, 4 of the 5 participants in the 50 mg of modafinil condition displayed a marked decline in comparison performance on the 2nd night. Second, a close examination of each panel in Figure 4 shows that, during the 2nd night, the 50 mg of modafinil condition consistently displayed the poorest performance. The latter result is further qualified by the fact that the Latinization employed in the design of the study was such that different participants took this dose on different weeks of the study. Thus, the result in question may be anomalous, or it may indicate a general nonmonotonicity in the function relating modafinil dose and cognitive performance during sleep deprivation (for a related discussion concerning the effects of pemoline on cognitive performance during sleep deprivation, see Babkoff et al., 1992, pp. 261–262).

## DISCUSSION

This study demonstrated that 300 mg of modafinil (100 mg/8 hr) can effectively maintain cognitive task performance at or near baseline levels during 64 hr of sleep deprivation under a more demanding work–rest schedule than that employed in related studies (e.g., Bensimon et al., 1991; Lagarde & Batejat, 1995). This result is encouraging because it approximates the administration schedule currently being prescribed for the treatment of idiopathic hypersomnia and narcolepsy (Billiard et al., 1994; Laffont et al., 1994). Subjective reports provided by the participants during the weekly debriefing sessions also revealed no evidence of intolerance or any symptomalogical manifestations under any of the dosing schedules. Hence, 300 mg of modafinil (100 mg/8 hr) appears to provide a safe and effective countermeasure to fatigue and declining cognitive performance during a period of prolonged sleep deprivation.

Although 300 mg of modafinil (100 mg/8 hr) clearly outperformed the alternative drug conditions on each of the measures that showed a sleep-deprivation effect, a systematic dose–response curve was not clearly evident for each measure. For example, for several measures (e.g., alertness, serial reaction time), 50 mg of modafinil closely paralleled 150 mg of modafinil, whereas for other measures (e.g., motivation, short-term memory), 50 mg of modafinil was virtually indistinguishable from the placebo. These results are suggestive in that performance on a specific cognitive task may be linked to a specific level of arousal or motivation that is produced by a stimulant. On the other hand, as previously mentioned, on the 2nd night, the 50 mg of modafinil condition displayed the poorest performance of all the conditions in the study. This suggests that, at least for the relatively low doses

investigated in this study, there exists a nonmonotonic dose function for modafinil resulting in a more variable performance profile across the various subjective and objective measures of sleep-deprivation stress.

Finally, although modafinil (100 mg/8 hr) has shown promising results in this study, it remains to be determined if this dosing schedule can prevent the more pronounced deficits in cognitive performance that are evident in sustained operational paradigms. Encouragingly, a direct comparison of performance in the placebo condition of this study with that of the placebo condition in the Pigeau et al. (1995) study (e.g., serial reaction time and short-term memory) revealed highly commensurate effects at the times tested. On the other hand, some of the more pronounced effects on cognitive performance in the Pigeau et al. study occurred at times (e.g., 0400–0800) during which the participants were not tested. Accordingly, a sustained operations study of modafinil (100 mg/8 hr), perhaps in comparison with other relatively safe fatigue countermeasures, such as tyrosine (Neri et al., 1995) and pemoline (Babkoff et al., 1992), may provide an important direction for future work on stimulant use in sustained operational contexts.

## ACKNOWLEDGMENTS

This study was funded by the French Ministry of Defence (DRET Contract 94/15). We thank the three reviewers for their helpful commentaries, Andrea Hawton for her graphical expertise, Chad Berry for his help in preparing the data files for analyses, Marc Grushcow and NTT for developing the portable cognitive test battery, and the technical support staff at the Centre de Recherches du Service de Santé des Armées for their assistance in conducting the study. Finally, sincere gratitude to the following people for their marvelous hospitality while Joseph V. Baranski was a visiting scientist in Grenoble: Alain and Valerie Buguet, Alain and Brigite Montmayeur, Corinne Cian, and Dominique Esquivié.

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